Preimplantation Embryos, Research Ethics, And Public Policy

by Carol A. Tauer

The NIH Human Embryo Panel, established in 1994, included members of various disciplines—science, ethics, law, medicine, public policy, as well as representatives of persons and groups that could be affected by the proposed research—all who worked together to recommend ethical guidelines for human embryo research. In this first-person account, the author describes the workings of such a panel, the method of deliberation, and the outcomes.

The NIH Human Embryo Panel, an advisory group established by the National Institutes of Health, met for five months in 1994 to recommend ethical guidelines for human embryo research. Participation on that panel was a concrete experience in engaging bioethical theory with pressing issues of public policy. Undoubtedly one of the major challenges for bioethics today is the development of a rational policy for research in areas that are politically sensitive as well as ethically complex.

When I agreed to serve on the NIH Human Embryo Research Panel, I agreed to be part of a process that would be difficult, perhaps stressful and frustrating, and possibly even fruitless. In certain respects those expectations were all fulfilled.

The Human Embryo Research Panel was established by NIH because Congress had given it the authority to fund research involving in vitro fertilization (IVF). Since IVF involves the laboratory fertilization of eggs by sperm, the resulting embryos undergo their first few days of development in the laboratory setting under the supervision of scientists. Thus the technique makes it possible to study the process of fertilization, as well as early embryonic development, in order to gain a better understanding of both normal and abnormal development.

Until recently, all knowledge we had about the earliest stages of human development was gleaned from animal models and extrapolated to the human case. In fact, most procedures used in applying IVF and other assisted reproductive technologies to humans had simply been transferred from practices with laboratory or domestic animals. When the Human Embryo Research Panel first met in February 1994, scientists told us we had to do better than that. A vivid memory from the first meeting of the panel was a lecture by embryologist Jonathan Van Blerkom, who described the state of science in the area of IVF and embryo research. He presented a dismal picture of shoddy research practices—flawed experimental designs, too small sample sizes, lack of control groups—so that results were often confusing and contradictory. As a result, IVF and other reproductive technologies continued to be inefficient (a low success rate), unnecessarily costly, and often associated with health risks to women and prospective children. Van Blerkom and others believed that this situation was at least partly due to lack of federal funding and standards for infertility research. In the absence of such federal involvement, research was generally conducted in private settings, as a corollary to providing services to infertile couples seeking help. Basic re-

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search, peer-reviewed research, replicability of protocols, and other practices considered essential in upholding research standards, all suffered in this situation.

How did such a situation occur? In 1978, coincidentally the year the first IVF baby was born in England, an Ethics Advisory Board was established in the United States to study in vitro fertilization. The EAB met for two years and issued a report concluding that research on IVF was ethically acceptable for federal funding. Requirements included that research be aimed at establishing the safety and effectiveness of IVF as a method of assisted reproduction, that egg and sperm donors be fully informed and consent to the research, and that embryos not be maintained in the laboratory beyond fourteen days' developmental age.

This report, if implemented, would have permitted federal funding of IVF research at the time that the procedure was first beginning to be used. However, the EAB report elicited an outpouring of letters opposing any such research and no research was ever funded. The EAB was dissolved in 1980, with its report simply shelved.

The 1994 Human Embryo Research Panel was an effort to resume the work that had been dropped in 1980. Under the NIH Revitalization Act of 1993, NIH was authorized to go ahead with the funding of IVF and early embryo research. However, the agency decided to move cautiously and to delay any funding until ethical guidelines could be developed by the Human Embryo Research Panel, approved by the Advisory Committee to the Director, and accepted by the Director of NIH.

The Process and Its Critics

The Human Embryo Research Panel met once a month from February through June 1994, usually for two days each time. At early meetings there were formal presentations by scientists, ethicists, and lawyers, including both invited experts and members of the Panel itself. Later meetings were largely devoted to reviewing drafts for the proposed report, identifying unresolved issues, debating these issues, and voting on questions where the Panel was divided.

All meetings were open to the public and the media, and no Panel business could be transacted in private. At each meeting two hours were available for ten-minute testimonies from members of the public; every person who wished to speak to the Panel was provided time. Some presenters were people struggling with infertility or inheritable genetic diseases, some represented professional organizations like the American College of Obstetricians and Gynecologists, but most were individuals who were ardently opposed to any research involving the study of early embryos in the laboratory. Some opponents were ill-informed as to the nature of the research the Panel was discussing; others expressed strong religious or moral reasons for their opposition.

Besides listening to members of the public, we received tens of thousands of written communications. Most were sent to the Panel as a whole, but large numbers were also mailed to individual members. The majority of these communications appeared to be linked to organized campaigns (for example, by right-to-life organizations), since the wording was identical on hundreds of them. However, the letters showed that there was strong opposition to federal funding of any research involving early embryos. Criticism was also directed at the composition of the Panel itself. The nineteen members of the Panel were chosen by NIH staff because of their expertise or experience in areas that could contribute to the work of the Panel. Our membership included physicians, scientists, lawyers, ethicists, and public policy scholars, as well as representatives of persons and groups that could be affected by the proposed research. While balance was sought (gender, racial, geographic), Panel members were not appointed on the basis of the particular positions or ideologies they subscribed to. In fact, at the time of appointment none of us was asked whether we did or did not support IVF or human embryo research.

Critics of the composition of the Panel argued that some persons who categorically opposed

embryo research should have been included. If this had been the case, the Panel's report probably would have turned out much the same as it did, but there would have been something like a minority report dissenting from the recommendations. As it was, all Panel members were able to agree to the report as a whole, even though on many individual points there had been a divided and even close vote. Dissents that are formally expressed within the Panel's report refer to very specific points of disagreement and are few in number.

From a philosophical point of view, the question of the moral status of the preimplantation embryo is highly complex and the subject of enormous debate.

The most difficult task the Panel faced was developing a moral framework to support the recommendations to be formulated. The Panel restricted its considerations to the preimplantation embryo, or the embryo that has never been transferred to a woman for possible implantation. From a philosophical point of view, the question of the moral status of the preimplantation embryo is highly complex and the subject of enormous debate. Depending on one's presuppositions and philosophical assumptions, a vast variety of positions can be taken.

The Panel tackled this controverted issue and included a chapter, "Ethical Considerations in Preimplantation Embryo Research," in its final report. The chapter includes a survey of a number of widely-espoused views on embryo status and it notes limitations of each of them. The authors then develop a position that can be expressed without reference to any particular religious, theological, or philosophical frameworks; thus, a position that might be convincing and acceptable as a basis for the formation of public policy.

Such a position may rely only on facts, on scientific knowledge, and on arguments that are coherent, understandable, and persuasive within the public policy context of a pluralistic society. Many people doubt that it is possible to develop arguments about the status of the embryo that are truly independent of all philosophical or theoretical presuppositions. There is no completely objective point of view, and a "view from nowhere" is nonexistent. Yet it is essential to enunciate broadly-acceptable moral arguments when the public policy arena requires them as a foundation for practical ethical guidelines and regulations.

The Panel's attempt to formulate such arguments may not be entirely satisfying, but we thought it was better to try to do so than to adopt avenues that have been chosen in other documents: either to invoke public opinion (as shown by surveys or some other measures); or merely to present conclusions with the caveat that we can agree on the conclusions even if we do not agree on reasons for supporting them. (I suspect, however, that the latter may represent some of the actual dynamics of the Human Embryo Research Panel. While no Panel member objected to the report's chapter on the status of the preimplantation embryo, discussion at meetings suggested that individual panelists did approach the issue in divergent ways. Some panelists regarded the final report as essentially a compromise between permissive and restrictive views on the moral status of the preimplantation embryo.)

All Panel members agreed with the summary statement on moral status that underlies the Panel's approval of some forms of embryo research:

> *Although the preimplantation human embryo warrants serious moral consideration as a developing form of human life, it does not have the same moral status as an infant or child.*

This statement was revised frequently and was

constantly checked against scientific information about the embryo from fertilization until the appearance of the primitive streak, about fourteen days' development. During this developmental stage, the following scientific facts apply:

(1) Twinning of the embryo is possible, and at least through the morula stage, several embryos may aggregate ("recombine") to form one embryo. Thus we do not have an individuated human organism at this stage.

(2) Before the appearance of the primitive streak, the entity represents a cellular level of life, wherein each cell has equal potential to develop into any tissue or organ of the fetus, or more likely, not to become part of the fetus at all. The primitive streak marks the beginning of the differentiation of cells into various types of tissues and organs.

(3) Before the appearance of the primitive streak, there is no neural tissue. Hence there is a lack of even the possibility of sentience and most other qualities associated with the moral status of persons.

(4) In normal procreation, during the period between fertilization and the completion of implantation a large proportion of embryos (generally estimated at over fifty percent) are discarded naturally. Theologians and philosophers have drawn implications from this prodigality of nature in making assessments of the status of the preimplantation embryo.

These four considerations carried differing weights with different Panel members. Some members who were most impressed by (3) thought it would be permissible to extend research slightly beyond the appearance of the primitive streak. Those who have followed discussions in Catholic theology in recent years were probably most influenced by (1) and (2), as these factors have been used to support the claim that the preimplantation embryo cannot be a human person with the claims that full personhood carries.[1]

Given the Panel's agreement that the preimplantation embryo does not have the moral status of a full human subject, we then had to determine whether we nevertheless ought to treat it as such. (Note that the federal regulations on research with the fetus, defined as the product of conception from implantation on, essentially do treat the fetus as a full human subject. Since these regulations apply to a stage later than the preimplantation stage and also involve an established pregnancy, there are good ethical reasons for regarding the fetus, so defined, as a protectable human subject. We had no quarrel with the ethical basis for current federal regulations on research with fetuses and our recommendations are not inconsistent with these regulations.) While some Panel members may have felt that the status of the preimplantation embryo was so insignificant that any worthwhile research would be permissible, that did not end up being the Panel's position. Vocal and committed panelists continually challenged us to evaluate the goals of research. What sorts of goals would be sufficiently compelling to justify infringing on the existence of the early embryo, limited though its status might be? We had, after all, agreed that the embryo warranted "serious moral consideration as a developing form of human life." What research goals would be so important as to override this claim to consideration?

The scientists and clinicians on the Panel, as well as invited experts, demonstrated to the Panel that important areas of human life and health were at stake. The panel was aware, of course, that research in infertility treatment and assisted reproduction had received no federal support and thus was not progressing as well as it could have been. As a result, infertile couples were perhaps missing opportunities to have children.

What we did not realize at first was that harms were occurring, risks were being imposed, through current practices in infertility treatment. For example, a woman currently preparing for assisted reproduction is usually given high doses of hormones to stimulate maturation of eggs in the ovarian follicles. Women who donate eggs to infertile couples also undergo hormonal

stimulation in order to provide large numbers of mature eggs ready for fertilization. These practices impose short-term risks and harms from excessive hormonal stimulation. Moreover, recent studies suggest possible long-term risks, including a significantly increased probability of ovarian cancer in women who were exposed to large doses of fertility drugs, particularly if repeated over a number of cycles.

We also learned that scientists do not have reliable measures as to whether a particular woman's eggs are capable of developing after fertilization, nor tests to determine which fertilized eggs are capable of developing into fetuses. Assisted reproduction is based on trial-and-error attempts and some women may be undergoing strenuous and risky procedures that offer no hope of achieving pregnancy for them.

The Panel became aware of the huge increase in multiple-gestation pregnancies that has occurred as a result of infertility treatment. Multiple births occur 22.4 percent of the time in women in infertility treatment, compared with 2 percent in the general population. The majority of these result from administration of fertility drugs to induce the ovulation of numerous eggs that are then fertilized through natural intercourse. Most others occur because three or more fertilized eggs were returned to the woman as part of an IVF procedure. Given the inefficiency of IVF and the fact that only a small percentage of transferred embryos usually implant in the uterus, the decision on how many embryos to transfer involves a compromise between risk and effectiveness.

Yet if three or more embryos actually implant, the pregnancy is high-risk by definition. Premature birth is much more likely, with an associated increase in the probability of infant morbidity and mortality. Patricia McShane, MD, director of IVF America-Boston, says that "The major health risk involved in infertility treatment is premature birth." Multiple-gestation pregnancy is also much harder on the mother. Lengthy confinement to bed may be necessary, and reportedly about sixty percent of IVF births are cesarean. A couple with a triplet or higher pregnancy is often presented the option of "selective reduction," whereby one or more fetuses are terminated prenatally for the sake of the others. This option requires the couple to make an excruciating moral choice, due to a problem caused by treatment aimed at helping them get pregnant.

Examples of risks and harms currently associated with assisted reproduction, problems that might be avoided through systematic programs of basic and clinical research, persuaded the Human Embryo Research Panel that there were compelling reasons for federal support of research. In particular, some types of research were not well-suited to the private sector and actually required federal involvement, as is true of medical and scientific research in general.

Some members of the Panel were reluctant to encourage federal support for infertility treatment, perceiving the need for a biological child as a personal preference and medical solutions as "elective." But scientists informed us that research connected with in vitro fertilization had applications in many areas connected to human health and disease. These areas include the transmission of genetic diseases, the etiology of birth defects and cancers, and the use of underdeveloped cells for the repair of injured and debilitated tissues and organs.

Work on genetically inherited diseases is moving rapidly because of the high level of government funding allocated to the Human Genome Project. As it becomes possible to identify more genes responsible for inheritable conditions and diseases, the next question is what to do about the identified genetic anomalies. Until a cure is found, the back-up option is early diagnosis followed by treatment to minimize the effects and symptoms of the disease in question. The option of prenatal diagnosis may also be offered, so that a couple may choose whether to abort a pregnancy if the fetus is affected. Deciding whether to terminate a pregnancy that is well underway is painful both psychologically and morally for prospective parents.

Advances in genetics are making it possible to

consider diagnosing genetic diseases within the first few days after in vitro fertilization. When the preimplantation embryo is at approximately the eight cell stage, one or two cells may be removed without damage to the remaining embryo. Karyotyping these cells provides a diagnosis of the genetic health or normality of the embryo from which they were taken. Thus if a couple at genetic risk has had a number of eggs fertilized, those that are healthy could be distinguished from those that are not. A couple who would not want to abort an established pregnancy may feel differently about simply not transferring genetically compromised embryos to the woman two or three days after fertilization.

While the Human Embryo Research Panel did not deal with the topic of human gene therapy (a permanent subcommittee has been established at NIH for that purpose), the Panel was aware of potential implications. All gene therapy to date has been somatic, that is, directed to curing or ameliorating the condition of a sick individual. A more radical type of gene therapy that has been debated but not yet attempted is germline therapy, or a remedy that would be passed on to future generations and would prevent descendants from having the disease. But germline therapy is possible only through directly modifying germ cells (eggs and sperm) or undifferentiated embryos. Thus if any germline gene therapy were approved, it most likely would involve research with in vitro fertilized embryos.

Scientists also reported to the Panel that simply learning more about the process of fertilization and what can go wrong during the earliest days of development was essential for progress in preventing birth defects. Moreover, there is evidence that some illnesses that develop later, for example, some childhood cancers, may have roots in early embryonic development. Scientists have relied heavily on the study of animal models to learn about human embryological development. While such studies are a necessary prelude to human studies, they cannot totally replace specifically human research.

One of the most surprising human benefits anticipated from in vitro fertilization research is a therapeutic application of cell lines derived from embryonic cultures. Research with cells taken from mouse embryos at the blastocyst stage (predifferentiated) suggests that these cells could be stimulated to differentiate into desired types of tissue, depending on what was added to the culture medium. These embryonic "stem cells" hopefully could be progenitors of cell lines that could replace damaged tissue in a child or adult; for example, neural cells for spinal cord repair or Parkinson's disease. Because embryonic stem cells are at such an early developmental stage, they behave differently from mature cells of the same tissue type, and might actually bring about regeneration of damaged functions.

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Some critics of the Human Embryo Research Panel assert that the Panel's recommendations rely too heavily on claims of scientific promise, and that the report subordinates any moral consideration due the early embryo to utilitarian goals. Rather, the Panel believed that the preimplantation embryo ought not be subjected to research except for extremely good reasons. Thus, the embryo's claims are not absolute, even though they are substantial. In order to determine what sorts of research would be significant and compelling enough to allow studies of in vitro fertilization and the resulting embryos, the Panel had to become knowledgeable about current practices in assisted reproduction, as well as about prospective advances in infertility treatment, genetics, and therapeutic modalities.

The Panel agreed most strongly that research should be permitted in order to remedy problems

currently present in the practice of assisted reproduction in the United States, practices that impose unnecessary risks and harms, as well as obstacles to improved effectiveness and lowered costs. The Panel also believed that preimplantation diagnosis for genetic defects should be supported, and that studies of preventable birth defects and the origin of childhood diseases should be encouraged. Regarding more speculative advances in medicine, the Panel was more reserved and placed many of these research programs in the category, "Warrants further review."

In order to maintain due consideration for the preimplantation human embryo as distinctly different from the embryos of nonhuman animals, the Panel required: that all research be carefully scrutinized for its significance and scientific merit; that studies of human fertilization or human embryos be allowed only if it was not possible to do the research in any other way; that the number of embryos studied be restricted to the smallest number consistent with scientific validity; that embryos not be preserved in the laboratory for longer than required by the aims of the specific research protocol; and that in no case could embryos be retained in the research setting past fourteen days' developmental age, the usual time of appearance of the primitive streak.

The Political Aftermath

The Human Embryo Research Panel submitted its report on September 28, 1994, and on December 2, the Advisory Committee to the Director of NIH unanimously approved the entire report. Late that same day, however, President Clinton issued a statement in which he thanked the Panel for its work at the same time as he overruled a key portion of the recommendations. The statement read:

> " I do not believe that federal funds should be used to support the creation of human embryos for research purposes, and I have directed that NIH not allocate any resources for such research."

This statement was a surprise to members of the Panel, which had had no indication that the Administration subscribed to a position on its work or wished to place any constraints on it. Also, while much of the research we thought important could still be funded, either in the course of clinical infertility treatment or using embryos remaining from infertility treatment and donated by progenitor couples, still some important research depended on being able to study the process of fertilization itself. Some crucial research, for example, studies of laboratory maturation of eggs and the freezing of eggs, required fertilization as the endpoint of a sound research program. It would be necessary to establish whether the matured or frozen eggs were fertilizable and would cleave and develop normally.

Though disappointed, Panel members consulted among themselves and with NIH staff in hopes of separating out the recommendations that were still viable so that NIH could scrutinize, approve, and fund some of the proposals that were pending. This separation was a difficult task, since the various aspects of the Panel's report were all interrelated, but the President's mandate made it imperative to proceed in this fashion.

At the present time (early October 1995) it is not clear whether NIH will be able to fund any IVF or embryo research. With more conservative membership than in 1993, the House of Representatives has recently moved to rescind the provision of the NIH Revitalization Act that allowed federal funding of research involving IVF. On August 3, 1995, the House voted to attach an amendment to the appropriations bill for Health and Human Services that would ban federal funding for all human embryo research.

Some ranking members of Senate committees (for example, Mark Hatfield, R-Oregon, chair of the Appropriations Committee, and Arlen Specter, R-Pennsylvania) have indicated their opposition to using appropriation bills to advance positions on social issues and agendas. The Senate appropriations bill for Health and Human Services has been reported out of committee without any such amendments attached. At the time that the bill comes up for Senate vote, a floor amendment banning federal funding of embryo

research is anticipated. However, it is uncertain whether such an amendment will prevail in the Senate as it did in the house.

Once again we are in the situation that followed the disbanding of the Ethics Advisory Board in 1980. Research involving in vitro fertilization and preimplantation embryos has once again been investigated by a blue-ribbon federal panel; it has once again been found ethically acceptable under careful restrictions and supervision. Once again, however, the possibility of federal funding seems to be on hold.

The experience of the Human Embryo Research Panel shows that ethics can be done in a public setting and a pluralistic society and that conclusions can be reached in a rational, fair, and responsible way. But the aftermath suggests that it may not be equally possible to implement ethical recommendations when they run counter to the beliefs of a committed portion of the citizenry.

Endnotes

1. See, for example, Richard A. McCormick, S.J. 1991. "Who or What is the Preembryo?" *Kennedy Institute of Ethics Journal* 1: 1-15; and Norman M. Ford. 1989. *When Did I Begin?* Cambridge: Cambridge University Press.

For a free copy of the Human Embryo Research Panel Report, contact:

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